Alterations in small arterioles precede changes in limb skeletal muscle after myocardial infarction

D. Paul Thomas, Olga Hudlicka, Margaret D. Brown, and Durmus Deveci. Alterations in small arterioles precede changes in limb skeletal muscle after myocardial infarction. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H1032–H1039, 1998.—We tested the hypothesis that alterations in arterioles in locomotor skeletal muscles in rats with myocardial infarction (MI), but before development of congestive heart failure (CHF), precede structural and functional changes commonly observed in limb muscle in association with CHF. Resting diameters of third- (A3) and fourth-order arterioles (A4) in extensor digitorum longus (EDL) muscle were significantly exaggerated vasoconstrictor response to norepinephrine (10−8, 10−7, and 10−6 M) compared with control animals. Dilation of A4 in response to 10−4 M adenosine was significantly attenuated in both groups (P < 0.05), whereas dilation of A3 was unaltered. Microvessels from both groups of infarcted rats constricted to all doses of acetylcholine (10−9, 10−8, and 10−7 M) and showed a significantly exaggerated vasoconstrictor response to norepinephrine (10−9, 10−8, and 10−7 M) compared with microvessels in control rats (P < 0.05). Peak isometric tension of combined tibialis anterior and EDL muscles and muscle fatigue (final/peak tension × 100), measured during 5-min isometric supramaximal twitch contractions at 4 Hz, were similar in control and MI rats (218 ± 7 vs. 213 ± 15 g/g muscle and 52 ± 1 vs. 51 ± 9%, respectively; n = 5 for both). There was also no difference with respect to the proportion of oxidative fibers or capillary-to-fiber ratios. Our results indicate that, in rats with left ventricular dysfunction but without failure, decreased diameter and perturbations in reactivity of small arterioles precede alterations in skeletal muscle performance often seen at a later date in association with CHF. These findings are consistent with the notion of aberrant endothelial and smooth muscle function and may contribute to the maintenance of blood pressure after MI but before CHF.

endothelium; nitric oxide; heart failure

A consequence of myocardial infarction (MI) leading to congestive heart failure (CHF) in both humans and animals appears to be limb muscle fatigue. This fatigue is most clearly demonstrated in response to increasing levels of exertion (24, 32), which has, in part, been attributed to reductions in blood flow to the skeletal musculature during exercise (24, 37, 38). Although there are a number of studies supporting this concept, it has also become evident that abnormalities intrinsic to muscle itself are associated with CHF (2, 6, 12). These abnormalities also manifest themselves readily during exercise or electrical stimulation and include increased phosphocreatine breakdown (2), reduced oxygen consumption at any given workload, and premature lactic acidosis (41). Additional alterations seen in CHF include muscle atrophy (22), fiber-type transformation (6), and reductions in capillary density (12) and in enzymes involved with both terminal oxidation and β-oxidation of fats (6, 12).

Initially, the cause of these abnormalities in skeletal muscle was attributed to impaired ventricular function and tissue perfusion (33). More recent findings have questioned this assumption, focusing instead on increased vasoconstrictor tone (7, 9), activation of the renin-angiotensin system (13), and endothelial dysfunction as playing a major role in the skeletal muscle perfusion deficits seen in CHF (8–11). However, these two points of view are not as divergent as they might at first seem, as shown early on by the findings of Zelis et al. (40) and more recently by Sullivan and Hawthorne (32). These investigators demonstrated that only with severe CHF is blood pressure significantly reduced in both humans and animals. Furthermore, a progressive increase in resting systemic vascular resistance is seen in patients that is linearly related to the reduction in cardiac output and severity of CHF (21). Likewise, in animal models of CHF, increases in total or hindlimb vascular resistance and corresponding reductions in skeletal muscle blood flow and vascular transport capacity are infarct size dependent (26). Chronic reductions in peripheral blood flow as seen in CHF are also thought to affect vascular endothelial function, resulting in attenuated nitric oxide (NO) release (11). In addition, severe reductions in blood flow per se have been shown to deleteriously affect muscle oxidative capacity and related enzyme activities (3). This chain of events refocuses attention on maintenance of blood pressure in the face of reduced cardiac output as being the first step in a vicious cycle that may ultimately lead to skeletal muscle dysfunction and failure.

In cases in which pump function is less seriously compromised post-MI, as seen with smaller infarcts, reductions in peripheral blood flow and increases in vascular resistance are less pronounced (26), and the metabolic abnormalities seen in muscles of severe CHF patients or animals may not be apparent (2, 6). However, even in the nonfailing, compensated left ventricle (LV) post-MI, neurally or hormonally mediated increases in arteriolar tone may, in the long term, lead to structural alterations of these vessels as reported recently (29).

Therefore, the objectives of this study were 1) to test whether locomotor skeletal muscle (extensor digitorum longus (EDL)) microvessel resting tone and reactivity is altered post-MI but without CHF, 2) to see whether any alterations observed are infarct size and vessel size dependent, and 3) to examine performance, oxidative characteristics, and capillarity in this same muscle to see whether they are altered before CHF. In this manner we hoped to evaluate whether MI-induced...
vasoreactivity abnormalities in small arterioles supplying muscle precede the metabolic derangements seen in muscle itself.

METHODS

Animal selection and infarct surgery preparation. Experiments were performed on young adult female Wistar rats in accordance with the Home Office Guidance on the Operation of the Animals (Scientific Procedures) Act 1986. All surgical procedures were performed under aseptic conditions. Rats were first divided into control and infarcted (MI) groups. Rats undergoing infarct surgery were anesthetized with a medetomidine (0.25 mg/kg)-ketamine (60 mg/kg) combination administered intraperitoneally, intubated, and placed on a rodent respirator (Harvard model 683). A chronic MI was then surgically produced as described in detail previously (23). Briefly, the heart was exposed through a left thoracotomy between the fifth and sixth ribs, and a pericardectomy was performed to allow visualization of the left anterior descending coronary artery, which emerges from beneath the left atrial appendage. A deliberate attempt was made to ligate this vessel 3–4 mm distal to the left atrium to produce small coronary artery lesions that supplied small arterioles to this muscle. Throughout these surgical interventions, muscle and skin incisions were immediately closed with separate purse-string sutures, and the lungs were fully expanded. All surviving rats received a broad-spectrum antibiotic (enroflaxacin, 2.5 mg in 1 ml) for 4 days postsurgery, and every attempt was made to minimize discomfort (buprenorphine, 2.5 µg in 0.1 ml twice daily) during this period. The mortality rate either from the surgery or during the first 24 h postsurgery was ~20% so that a total of 18 rats survived for subsequent intravital evaluation.

Intravital preparation and observation of muscle microcirculation. Ten to twelve weeks after MI surgery, both control (n = 11) and MI rats were anesthetized with the medetomidine-ketamine combination before surgical preparation of EDL as performed previously (15). In brief, the right jugular vein and carotid artery were cannulated for administration of additional anesthetic whenever necessary (pentobarbital sodium, bolus 5 mg/kg) and recording of arterial blood pressure, respectively, and the right hindlimb was prepared for exposure of the EDL muscle (36). During this procedure the EDL was partially rotated, which permitted evaluation of the arteriolar supply to this muscle. Throughout these surgical procedures, and during the subsequent observation period, the surface of the exposed muscle was continuously superfused with a warmed, deoxygenated Krebs-Henseleit solution (131.9 mM NaCl, 4.7 mM KCl, 1.17 mM MgSO4, 2.0 mM CaCl2, 2H2O, and 22.0 mM NaHCO3, pH 7.35–7.45) at a temperature of 32–34°C at 5 ml/min (15).

The animal was next placed under an intravital microscope (ACM, Zeiss, Oberkochen, Germany) fitted with a TV camera (Cohu 4712) connected to a video recorder (Panasonic VCR, NV-F70HQ), and arterioles were identified by means of a Leitz immersion objective (×25/0.6 na) using fiber-optic epi-illumination (Schott, Oberkochen, Germany). Images were recorded on the video recorder and displayed on a TV monitor at a final magnification of approximately ×1,000. With this magnification, monitor resolution was calculated as 0.45 µmpixel from measurements made using a graticule. The ability of the eye to perceive changes in location is far better than its ability to resolve two objects. Hence, actual errors are considered to be less than this value, with visual interpolation giving an effective resolution of <0.4 µmpixel. Both precapillary (A4) and the next highest order of arterioles (A3) were identified by their location within the branching microvascular network. Arteriolar luminal diameters (in µm) were measured by aligning vessel images on the TV screen in the vertical plane and superimposing a previously calibrated video reticle generator. Repeated measurements of the same vessel at various intervals gave virtually the same values. All reticle measurements were displayed on a chart recorder (Lectromed, Welwyn Garden City, UK) and saved on videocassette, on which time and frame counts were also recorded (15). A total of 30, 33, and 26 (A3) and 40, 43, and 25 (A4) EDL arterioles were measured from 11 control, 11 small MI (MI1), and 7 medium-sized MI (MI2) rats, respectively, and treated as independent observations. Luminal diameters were obtained both at rest and after randomized topical administration of 1 ml of 10−5 or 10−4 M adenosine (Ado), 10−6, 10−5, or 10−4 M acetylcholine chloride (ACh), and 10−6, 10−5, or 10−4 M norepinephrine (NE) (all from Sigma). Superfusate was used as the vehicle for these solutions, which were administered via syringe onto the muscle surface under the objective lens. Care was taken to keep the solutions without access to air as much as possible and to keep the temperature similar to that of the superfusion fluid. The drugs were administered over a 5- to 10-s period so that the actual concentration was lower due to dilution by the superfusate. Several minutes were allowed to elapse before administration of each subsequent dose/drug so that the diameter of the arteriole being evaluated had returned to resting values. Total duration of observation did not exceed 2 h, by which time there were no signs of deterioration of the preparation as judged by white blood cell adhesion to postcapillary venules.

Muscle performance. Immediately after all intravital observations were made, muscle performance of combined EDL and tibialis anterior (TA) muscles was evaluated in the contralateral limb in a subset of control and MI rats (n = 5 for both groups). The EDL and TA tendons were freed from skin and surrounding tissue, and the muscle segments were sharpened to a strain gauge (Dynamometer UF1, 16 oz) to record their combined isometric tension. With muscle length initially adjusted to give maximal contractions, indirect stimulation was applied (0.3-s pulse width, supramaximal voltage, usually 5–6 V) via bipolar silver electrodes to the distal end of the cut common peroneal nerve for 5 min at 4 Hz (15). Peak tension, usually attained ~30 s after the beginning of contractions, was taken to indicate maximal force-generating capacity. Muscle endurance capacity [fatigue index (FI)] was evaluated as final twitch tension/peak tension × 100. Muscle tension outputs together with arterial pressure recordings were displayed on a Lectromed recorder and captured on a computer (Royal 80486) via a PC-LMP-16 (National Instruments, Newbury, UK) analog-to-digital converter board.

Hemodynamic measurements. Immediately after the intravital studies (or muscle performance measurements) were made, a Millar 3-Fr microtip transducer catheter was advanced down the right carotid artery into the LV to continuously record LV end-diastolic pressure (LVEDP) and the peak first positive derivative of LV pressure (LV +dP/dt max). The LV pressure trace was temporarily switched to high gain (×10) to record end-diastolic pressure, which was measured as the inflection point in the diastolic pressure trace. LV +dP/dt max was derived from the LV pressure trace using an Electromed differentiator channel. After the comple
tation of all functional measurements, euthanasia was achieved by anesthetic overdose.

Skeletal muscle characteristics. The EDL was rapidly excised and weighed before histochemical analysis of succinic dehydrogenase (SDH) activity and capillarity. The muscle was sectioned in midbelly, rapidly frozen in liquid nitrogen-cooled isopentane, and subsequently sectioned in a cryostat. Twelve-micrometer-thick sections were stained for SDH to demonstrate oxidative activity by using the method of Nachlas et al. (27), and adjacent sections were processed to demonstrate all anatomically present capillaries, which were stained for alkaline phosphatase using 5-bromo-4-chloro-3-indolyl phosphate toluidine salt as substrate and tetrazolium as chromagen (42). Capillary supply was expressed as the capillary-to-fiber ratio (C/F) from counts made in 20 fascicles of muscles from 5 control, 4 MIs, and 4 MIm animals (15).

Determination of ventricular weights and infarct size. The heart was blotted and weighed after excision and removal of both atria. Both ventricles were then individually weighed after the right ventricular (RV) wall had been dissected away from its attachment to the LV septum. The entire LV was then immersion-fixed in 10% buffered formaldehyde for a minimum of 3 days before being cut into four transverse sections from base to apex in parallel with the atrioventricular groove. These four sections of the LV were in turn sectioned on a Vibratome (General Scientific), mounted onto gelatin-coated slides, and stained with van Giesen’s connective tissue stain so as to differentiate between scar tissue and viable muscle. These sections were magnified and projected, and the size of the infarcted area, expressed as a percentage of the combined endocardial and epicardial circumference of the LV, was determined by planimetry.

Statistical analysis. All data are presented as means ± SE. A one- or two-way ANOVA design was used as appropriate to permit calculation of all possible main effects as well as overall interactions (i.e., group-vessel type interaction effects). The Bonferroni t-test was used for post hoc analysis, and the 0.05 level of probability was used to signify statistical significance.

RESULTS

Body, LV, RV, and EDL weights. Despite attempts to match all groups by body mass, rats that underwent MI surgery and remained in the animal care unit for up to 3 mo before final experimentation were heavier than age-matched control animals delivered 1 wk before evaluation. For this reason, all heart and EDL weights were expressed in both relative and absolute units (Table 1). Even when corrected for body weight, LV weight was significantly higher (P < 0.05) in the MIm group compared with that in both MIs and control groups. This finding indicated a true hypertrophic significance.

Central hemodynamics and LV function. There were no differences in mean blood pressure or LVEDP among the three groups, although increases in LVEDP in the two infarcted groups bordered on significance (both P < 0.1) as shown in Table 2. The use of LV dP/dt max as an index of LV function also revealed a significantly depressed contractile state in both MIs and MIm hearts compared with controls.

Resting arteriolar diameters. Lumen diameter for both A3 and A4 arterioles in the three groups is shown in Fig. 1. Mean diameters in control rats were 7.5 ± 0.4 and 5.9 ± 0.3 µm for A3 and A4 vessels, respectively. The diameters of A3 arterioles were smaller in both MI groups, whereas the same comparison for A4 vessels showed a significant reduction only in the MIm group. However, there was no significant difference in arteriole diameters between the MIs and MIm groups.

Vasoactive responses. Compared with that in controls, dilation in response to 10⁻⁵ M Ado was attenuated in A4 microvessels from the MIm group (22.5 vs. 12.8% increase; P < 0.05) (Fig. 2). A higher concentration of Ado (10⁻⁴ M) resulted in a similar response in A3 vessels in all groups, but the vasodilator response was significantly attenuated in A4 from both infarcted groups. In addition, A4 arterioles in infarcted animals closed immediately after dilation, and flow would cease altogether for several seconds.

Although 10⁻⁹ M and 10⁻⁸ M ACh caused very little change in A3 or A4 vessel diameters in control rats, 10⁻⁷ M produced constriction (Fig. 3). In contrast, 10⁻⁹ M ACh produced a 31 and 27% constrictor effect on A3 arterioles in MIs and MIm rats, respectively, with values in A4 vessels of 28 and 20% (Fig. 3). At the next highest ACh concentration (10⁻⁸ M), A3 arteriolar response did not differ among the three groups, but A4 vessels from both infarcted groups were significantly more constricted. At 10⁻⁷ M, ACh constricted all vessels, but A4 vessels from the MIm groups were still more constricted than control vessels.

NE constricted both A3 and A4 vessels in a dose-dependent manner in control rats (Fig. 4). However, this response was significantly exaggerated to all doses of NE in both MI groups, with no differences between MIs and MIm rats. Thus, in response to 10⁻⁷ M NE,
Table 2. Infarct size and central hemodynamics in control rats and rats with small and medium-sized infarcts

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>MI Size, %LV</th>
<th>MAP, mmHg</th>
<th>LVEDP, mmHg</th>
<th>LV + dP/dt\text{max}, mmHg/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>11</td>
<td>84 ± 4</td>
<td>3.1 ± 0.3</td>
<td>4,881 ± 286</td>
<td></td>
</tr>
<tr>
<td>MI_s</td>
<td>11</td>
<td>17 ± 2</td>
<td>83 ± 2</td>
<td>7.4 ± 2.2</td>
<td>3,187 ± 412*</td>
</tr>
<tr>
<td>MI_m</td>
<td>7</td>
<td>36 ± 1†</td>
<td>81 ± 4</td>
<td>6.1 ± 1.7</td>
<td>3,350 ± 545*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of rats. MI size, infarct size; MAP, mean arterial pressure; LVEDP, LV end-diastolic pressure; LV + dP/dt\text{max}, peak first derivative of LV pressure trace. *P < 0.05 vs. control; †P < 0.05 vs. MI_s.

although control A3 vessels were still 25% patent, these same vessels in MI_s and MI_m vessels were virtually closed. A similar difference in response was also seen in A4 arterioles (−70% vs. −96 and −94%, respectively; both P < 0.001).

Muscle performance and FI. Tension curves generated from EDL and TA muscles during 5-min isometric twitch contractions were similar in control and MI groups (Fig. 5). The MI group included both MI_s (n = 3) and MI_m (n = 2) animals, with a mean infarct size of 28 ± 4%. Peak twitch tension during 5-min stimulation period in control and MI groups was not different (218 ± 7 vs. 213 ± 15 g/g muscle wet wt, respectively), and the muscles fatigued to the same extent over time (FI = 52 ± 2 and 51 ± 9%, respectively).

EDL oxidative characteristics and capillary supply. Neither muscle capillarity expressed as C/F nor percentage of oxidative fibers as assessed by SDH staining was different among any of the three groups. C/F was 1.38 ± 0.06, 1.47 ± 0.03, and 1.49 ± 0.2 for control, MI_s, and MI_m animals, respectively. The percentages of histochemically stained oxidative fibers for the same three groups were 55.1 ± 2.8, 52.3 ± 0.9, and 59.8 ± 3.7, respectively.

DISCUSSION

It is now recognized that alterations in peripheral vascular smooth muscle and endothelium play a role in abnormal resting vasomotor tone, vasoreactivity, and blood flow response to various stimuli in CHF patients and animal models (1, 7–9) and that these changes may contribute to increased muscle fatigue in CHF. In human studies, these conclusions are based on evaluation of perturbations in upper- or lower-limb blood flows and resistances after both pharmacological and functional interventions such as exercise (1, 9). In animal CHF models, similar conclusions have been reached when blood flow deficits to individual muscles have been estimated using microspheres (26). The site of vascular control is in the arterioles, and these vessels have been shown to be sensitive to both endothelium- and non-endothelium-mediated agonists. Although Didion et al. (7, 8) have shown that arterioles with a diameter of 40 µm dilate less and constrict more in response to endothelium-dependent dilators and constrictors in a spinotrapezius muscle preparation in rats post-MI, there are no studies that have directly evaluated vasoreactivity of resistance vessels as opposed to conduit vessels in limb skeletal muscle after infarction.
Moreover, it is not known whether the reactivity or diameters of terminal arterioles are altered and whether such alterations occur in animals without any signs of heart failure and with relatively small infarcts. We hypothesized that, in an attempt to maintain blood pressure, neurogenic, hormonal, and local influences would affect both smooth muscle and endothelial function of these arterioles and that these changes might precede metabolic and contractile alterations seen in locomotor muscle perfused by these microvessels.

The most significant finding from the current study is that abnormalities in limb skeletal muscle microvasculature can be detected in the rat model of MI with LV dysfunction but without congestive heart failure. With this degree of pathology, and at the time point chosen, muscle structure and function appeared unaffected, at least as evaluated by gross size, capillarity, and oxidative characteristics as well as by tension-generating and fatigue properties.

Changes in microcirculation. Resting diameters of A3 and A4 arterioles in EDL from control rats were smaller than those in cremaster (14, 16) or spinotrapezius muscle (8) but were comparable to values reported in the same muscle previously (25). Changes in microvessels associated with MI included smaller diameters and altered responses to vasoactive agents. The reductions in resting diameters induced by MI in the present study support previous findings of elevated resting limb vascular resistance and reductions in limb blood flow in this same model (5, 26) as well as in human CHF patients (9, 32).

Arteriolar reactivity. Dilation in response to Ado was smaller than has usually been found in somewhat larger (20–30 µm) arterioles in other muscles (28). This can be explained by the mode of administration of the drug, which was diluted, and by the fact that we were working with a muscle in which the arterioles are not on the surface. Thus less Ado reached the vessels than in a flat muscle such as the spinotrapezius, and possi-
bly even less reached the endothelium. Whether the significant attenuation in dilatation to both concentrations of Ado in the terminal arterioles of MI rats indicates only smooth muscle adenosine-receptor sensitivity changes is a point of some controversy (4, 20). Indeed, partial endothelium-dependent vasodilator action of Ado has been demonstrated previously (4) and could implicate alterations in the NO release pathway and/or adenosine receptors associated with endothelial cells (36). Because we were not able to verify whether vessels were maximally dilated in response to the highest level of Ado administered, the attenuated dilation seen in terminal arterioles could indicate heightened vasoconstrictor tone or even structural changes of these vessels (29). The diminished sensitivity to Ado seen in the current study highlights the potential role of A4 arterioles in muscle hypoperfusion during high flow states such as exercise, previously documented in CHF (26).

Absence or attenuation of a vasodilator response to ACh has been interpreted as an indication of impaired endothelial function. It is now well accepted that endothelial dysfunction is associated with CHF, and this has been shown in vitro in isolated ring segments of major arteries (34) and in vivo by an attenuated limb blood flow response to ACh-stimulated NO release as well as to exercise (10, 26). We chose to assess the ACh-stimulated response because previous findings with respect to basal release of NO in CHF are somewhat equivocal (10, 11, 34). Although ACh, surprisingly, did not produce dilation at the level of A3 and A4 arterioles in control muscles, muscle perfusion was enhanced as evidenced by easily visualized increases in red blood cell velocity through individual capillaries supplied by these arterioles. This finding indicates possible dilation of arterioles upstream to the site of measurement, in agreement with previous observations (25). No change or a decrease in the diameter of these very small arterioles, which have heretofore not been evaluated for their reactivity to ACh, is possibly due to the fact that ACh is acting principally on smooth muscle, where it has been shown to produce constriction in some vascular beds (17). As noted above, arterioles in our preparation are not on the surface of the muscle, and administration by topical application, presumably lasting only a short time, does not necessarily ensure that ACh easily reached arteriolar epithelium.

ACh was seen to have a major dilator effect on higher order arterioles in a transilluminated spinotrapezius preparation (8), in which it can reach vessels very easily. In the study by Didion and Mayhan (8), this dilation was attenuated in rats with MI and heart failure. In our experiments, A3 and A4 arterioles showed more pronounced dose-dependent constriction in both MI groups than in control rats. These findings indicate a possible perturbation of the endothelial release mechanism for NO. This hypothesis is further supported by the findings of dose-dependent constriction to ACh and a change from dilation in response to Ado to constriction in EDL in experiments in which NO synthase was blocked by chronic administration of N\textsuperscript{G}-nitro-L-arginine (30).

The findings of increased sensitivity of both A3 and A4 arterioles to all three levels of NE employed in the current study also support the possibility of perturbations in endothelial function. Teerlink et al. (34) noted that the increased contractile response to NE of thoracic aorta rings taken from rats 1 wk post-MI was only seen in vessels with intact endothelium and that contractions were actually reduced in endothelium-denuded rings. These findings were interpreted as indicative of endothelial dysfunction with reduced basal NO release to counteract the adrenergic vasoconstrictor effect on \(\alpha_1\)-receptors. Tesfamariam and Cohen (35) showed that isolated arteries with damaged endothelium constrict more in response to NE, and Kaley et al. (16) demonstrated greater constriction of arterioles in rat cremaster muscle in response to NE after administration of N\textsuperscript{G}-monomethyl-L-arginine. Thus the increased constriction in response to NE post-MI in the
current study could be indicative of endothelial dysfunction (34) as opposed to alterations in circulating catecholamine level or smooth muscle adrenergic receptor sensitivity. Because NE activates both α1- and α2-receptors on vascular smooth muscle and α2-receptors on endothelium (37), with the latter attenuating constriction, enhanced constriction in MI rats could also be explained by modification of α2-receptors on endothelium.

Skeletal muscle. The resting diameter and vasoreactivity changes in third- and fourth-order arterioles in EDL muscle after MI that were observed in the current study thus precede the alterations seen in skeletal muscle itself with overt CHF (2, 12, 19). Whether the putative deficits in skeletal muscle perfusion implied by the findings of the current study eventually lead to alterations in muscle structure and performance at a later time point could not be evaluated with the current study design. However, Schieffer et al. (29) noted a reduction in capillaries and an increase in volume fraction of collagen in quadriceps femoris muscle 1 yr post-MI in rats with infarct size midway between the sizes of the two groups employed in the current study. They also found smooth muscle hypertrophy in the walls of resistance vessels ranging in lumen diameters from 80 to 200 μm in the same muscle. It is thus tempting to speculate a cause-and-effect relationship between the arteriolar changes observed shortly after MI in the present study and those seen at a later date in tissues perfused by these vessels (29).

Study limitations. Because of the time constraints imposed by our desire to simultaneously measure ventricular and skeletal muscle function, it was not feasible to expose the muscle to an optimal number of vasoactive agents. Thus it was not possible, in the current study, to clearly distinguish between MI-induced abnormalities in vascular smooth muscle and those relating to endothelial function. What is clear, however, is that dilator function of these vessels is impaired, and there is an increased tendency toward constriction some 3 mo postinfarction. In this regard, the use of nitrovasodilators in future studies evaluating microvascular function post-MI without CHF will be important.

In summary, we have documented alterations in microvessel resting diameter and vasoreactivity in arterioles supplying locomotor skeletal muscle post-MI but without CHF. Our results indicate an attenuated small arteriolar response to the vasodilator Ado as well as an exaggerated vasoconstrictor response to NE. The response to ACh of small arterioles in EDL muscle from infarcted rats was, in some instances, diametrically opposite that seen in control animal vessels, thus implying endothelial dysfunction in microvessels supplying limb muscle in this pathological model. Such dysfunction could be due to reduced production of NO described in CHF (16, 18). These findings indicate that alterations in precapillary arterial diameter and reactivity exist before documentation of heart failure but in concert with depressed LV function.

The mechanism(s) by which MI without failure causes alterations in microvascular function is presumably the same as that seen in CHF with both neuroendocrine and hemodynamic sequelae of reductions in cardiac output. Interestingly, reduced total limb blood flows even at rest were documented in rats with infarcts <30% of the LV by Musch and Terrell (26). Whether the measured reductions in resting arteriolar diameter imply only alterations in tone or whether structural alterations in these microvessels have already taken place, as seen later (29), was not tested for in the current study. Significantly, abnormalities in terminal arteriolar vasoreactivity seen 3 mo post-MI precede changes in skeletal muscle structure and function frequently observed at a later date associated with CHF and may contribute to the maintenance of blood pressure in animals with impaired pump function.

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